

Protocol NETI-HAA :

Intensive enteral nutrition in association with steroids in the treatment of severe acute alcoholic hepatitis: A Belgian multicenter randomized study

Introduction:

Acute alcoholic hepatitis (AAH) is characterized by hepatocellular necrosis, ballooning degeneration and an inflammatory reaction with many polymorphonuclear leukocytes, and fibrosis (Mezey E. Treatment of alcoholic liver disease. Semin Liver Dis 1993). The presence of a severe AAH was identified by the presence of a discriminant function (DF) ≥ 32 . DF ≥ 32 has been shown to prospectively identify patients with a 40 to 50 % risk of dying within 2 months (Ramond et al, NEJM 1992). The main treatment of AAH consists of abstinence from alcohol. Corticosteroids are generally recommended in patients with severe AAH. Indeed, a recent analysis of the individual data of the patients from the last three randomized controlled trials showed a significantly higher 1-month survival in corticosteroids compared to placebo treated patients with a severe AAH (Mathurin et al, J hepatol 2002). However, efficacy of this therapy is insufficient, since around 40 % of patients with a severe AAH do not respond to corticosteroids (Louvet et al, Hepatology 2007). Moreover, corticosteroids are still contraindicated in case of active infection or gastrointestinal bleeding, which are relatively common complications in those patients. Therefore, alternative therapeutic options are needed and must be a medical priority.

Alcoholic patients with severe AAH are frequently malnourished and usually remain anorectic for several weeks (DiCecco SR et al, Nutr Clin Pract 2006). Some data indicate that malnutrition is a factor of bad prognosis in this disease. Recent evidence was also provided that adequate enteral nutritional support might have an important impact on long-term survival in those patients (Cabr e et al, Hepatology 2000). However, up to now, no study evaluated potential synergetic effect of intensive enteral nutrition and corticosteroids. Moreover, in clinical practice, in the majority of the centers, patients with alcoholic hepatitis receive alimentary supplements and dietetic counseling, which is often insufficient and difficult to apply and to follow.

Aim :

To evaluate the effect of an intensive enteral nutrition (compared to clinical routine which consists in oral supplements) in association with corticosteroids in patients with severe acute alcoholic hepatitis.

Endpoints:

- **Primary** : 6 months survival
- **Secondaires** : 1 month survival, infection rate during hospitalisation, early bilirubin change (day 7), Lille score, development of hepatorenal syndrome

Setting:

Belgian multicenter randomized controlled trial (eventually also including French centers) under the auspices of the Belgian Association for the Study of the Liver (BASL).

Design: 2 arms trial, randomization 1/1

- **Groupe A** : Corticosteroids (Medrol 32 mg/d) for 28 days + intensive enteral nutrition by feeding tube for 14 days
- **Groupe B** : Corticosteroids (Medrol 32 mg/d) for 28 days + « classical » oral alimentation for 14 days

Central randomization by sealed envelopes (random code, blocks of 6 patients)

Inclusion criteria:

- Acute alcoholic hepatitis proven by a liver biopsy (necessary histological findings : neutrophils infiltration, ballooned hepatocytes and Mallory bodies)
- Presence of a severe disease, defined by a Maddrey score higher than or equal to 32, at screening and in baseline (day 0). Maddrey score = total bilirubin in mg/dl + 4,6 X (Prothrombin time patient in sec – prothrombin time control in sec)
- Age between 18 and 75 years old, extremes included
- Recent jaundice or in recent aggravation (less than 3 months)
- Chronic alcohol consumption (more than 40 g/day)
- Informed consent read, understand and signed by the patient (in case of significant encephalopathy, a family representative can signed in place of the patient)
- Maximal delay between admission and randomization of 10 days.

Exclusion criteria:

- Other disease compromising 6 months survival of the patient
- Positive HIV or HCV serology, positive HBs Antigen
- Uncontrolled bacterial or fungal infection (infection must be judged controlled for at least 3 days)
- Uncontrolled upper GI bleeding (bleeding must be controlled for at least 5 days)
- Type 1 Hepatorenal syndrome (creatinin upper than 2,5 mg/dl), as defined by Salerno F et al, Gut 2007;56:1310-1318
- History of bariatric surgery
- Pentoxyphilline therapy
- MARS therapy

Treatment:

Treatment can be started after pathological confirmation.

All patients will receive Medrol® (méthylprednisolone) 32 mg/day after randomization for 28 days. In addition, vitamin supplements of B1 and B6 (Befact F® 1/day or intravenous form if necessary). Méthylprednisolone will be stopped after 28 days without progressive decrease.

Patients randomized in « intensive enteral nutrition » arm will receive by feeding tube (with the use of a microsonde), and in continuous administration, 2 liters of Fresubin HP Energy (1500 kcal/liter, 75 gr prot/liter) for patients with a weight of more than 90 kgs (after ascites removal), 1.5 liters of Fresubin HP Energy for patients with a weight between 60 and 90 kgs, and 1 liter of Fresubin HP Energy for patients of less than 60 kgs. Patients with significant encephalopathy despite therapy against encephalopathy will receive Fresubin Hepa in place of Fresubin HP Energy (1300 kcal/liter, 40 gr prot/liter, 44 % branched AA). Duration of enteral nutrition by feeding tube will be 14 days. The adaptation to the targeted volume must be achieved in maximum 3 days. Enteral nutrition will be administered by nasogastric microsonde.

Patients randomized in « classical oral nutrition » arm (control arm) will receive usual meals (estimated at 1750 kcal/day; 70 g protein/day), and alimentary supplements between meals to achieve the ESPEN recommandations (35-40 kcal/kg/day; protein 1.2-1.5 g/kg/day) (Plauth et al, Clinical Nutrition 2006). Calories and proteins intake must be recorded daily.

In the study, the use of antibiotics will be allowed if prescribed for a documented infection, in case of suspected infection, in primary or secondary prevention of spontaneous bacterial peritonitis, but will be not allowed systematically in prevention of other infection. All antibiotic prescription will be recorded and the reason of prescription specified. In the same line, eventual corticosteroids arrest must be recorded and reason must be specified.

Pentoxifylline therapy is not allowed.

Hospitalisation duration will be of 14 days in minimum (during enteral nutrition period) after randomization.

Data recording:

Data will be recorded by a paper CRF (see attached CRF).

- At screening :
 - o Clinical records : weight, height, sex, temperature, ascites, encephalopathy, past medical history
 - o Usual biology : WBC (+ formula), hemoglobin, platelet count, prothrombin time in % and in seconds, INR, albumin, total bilirubin, transaminases, GGT, alkaline phosphatase, urea, creatinin, ionogram
 - o HIV and HCV serology, HBs antigen
 - o Blood cultures, urinalysis + culture, ascites culture and PMN numeration
 - o Chest X-Ray, liver ultrasound
 - o Liver biopsy
- At randomization: repeat clinical records and usual biology (same than screening)
- During therapy:
 - o Clinical records (D7, D14, D28) : same than screening
 - o Usual biology (D7, D14, D28) : same than screening
 - o Blood cultures, urinalysis + culture, ascites culture and PMN numeration, Chest X-Ray (D7, D14, D28 optional)
 - o Dietetic evaluation: Evaluation of ingested calories and proteins during the 14 days of the study (period of enteral nutrition)

- During Follow-up (optional) : Patients will be seen after 1 month, than monthly to 6 months (the frequency of the follow-up is under the investigator discretion, and will be done as usual in each center)
 - o Clinical records : same than screening
 - o Usual biology : same than screening
 - o Alcohol consumption : relapse or no, quantity must be specified
- Hospitalisation duration and eventual intensive care stay duration

Statistics:

Based on a 6 months survival of 55 % in control arm, and 75 % in intensive enteral nutrition arm, 98 patients must be included in each arm, considering an α error of 0,05 and β error of 0,2.

Expected inclusion period is 2 years, which means that around 100 patients will be included per year.

Randomization et medications:

Multicenter study, under the auspices of the BASL.

Coordinating Investigator: Christophe Moreno, Erasme Hospital

Randomization will be centrally performed at Erasme Hospital

When a patient is eligible for entering the study, the investigator of the concerned center will fax or email the completed screening form containing only patient's initials (Fax number: 02/555.82.36; email: christophe.moreno@erasme.ulb.ac.be or urc-gastro@ulb.ac.be)

If the patient is eligible, a confirmation fax or email, with a randomization number and random treatment arm will be sent within 24 hours.

CRFs and specific enteral nutrition (Fresubin HP Energy and Fresubin Hepa) will be available in each participating center. Each center will be resupplied when needed.

Medrol® therapy will be prescribed by the investigator in charge of the patient, but must be initiated the same day than nutritional therapy prescribed in the study

Financial support:

Medrol® therapy, hospitalisation and follow-up after hospitalisation will not be paid by the study, since the management corresponds to the standard clinical practice.

Fresubin HP Energy and Fresubin Hepa therapies will be provided.

An amount of 200 euros will be paid per enrolled patient at the center recruiting the patient by the BASL

Insurance will be paid by the BASL

Publications:

Investigators enrolling patients in the study will be informed to each publication or abstract. Association to a publication will depend of the contribution of each investigator. Author's order will be decided by the BASL and the coordinating Investigator. No publication or communication will be performed without the approbation of the investigators.

Participating centers :

CENTRE	Investigateur
ERASME	Moreno
Liège	Delwaide
Leuven	Laleman
UCL-St Luc	Starkel
GAND	Colle
Hôpital St Pierre	Mulkay
Brugmann	Lasser
Jolimont	Deltenre
ANVERS	Michielsen
BRUGES	Orient
Ambroise Paré	Hittelet
CHU Charleroi	Leenaerts
VUB	Reynaert
Citadelle	Brixko
St Joseph	Bastens